## Roark, Jessica

**From:** Gambel, Phillip
**Sent:** Wednesday, August 06, 2003 6:00 PM
**To:** Roark, Jessica
**Subject:** spontaneous abortion again

here a couple more

the first two are the same or similar folks

i did not include all of the citations, since i think you have them already

did NOT request from library

| Set | Items | Description |
|---|---|---|
| S1 | 707 | (SPONTANEOUS(W)ABORTION) AND MODEL? |
| S2 | 590 | S1 AND HUMAN? |
| S3 | 109 | S2 AND (CORRELAT? OR PREDICT?) |
| S4 | 72 | RD S3 (unique items) |
| S5 | 4 | S4 AND (DBA?) |
| S6 | 4 | RD S5 (unique items) |
| S7 | 0 | (SPONTANEOUS(W)ABORTION)(20N)(MURINE OR MOUSE) AND (CORREL-AT? OR PREDICT?)(10N)(HUMAN) |
| S8 | 7 | (SPONTANEOUS(W)ABORTION)(20N)(MURINE OR MOUSE) AND (CORREL-AT? OR PREDICT?) AND (HUMAN) |
| S9 | 5 | RD S8 (unique items) |
| S10 | 22 | (SPONTANEOUS(W)ABORTION)(20N)(MURINE OR MOUSE) AND (MODEL?) AND (HUMAN) |
| S11 | 20 | RD S10 (unique items) |
| S12 | 12 | SPONTANEOUS(W)ABORTION AND MISCARRIAGE AND DBA? |
| S13 | 6 | RD S12 (unique items) |
| S14 | 117 | SPONTANEOUS(W)ABORTION AND DBA? |
| S15 | 58 | RD S14 (unique items) |
| S16 | 19 | S15 AND HUMAN? |

11/7/20 (Item 16 from file: 73)
DIALOG(R)File 73:EMBASE


04817476 EMBASE No: 1991312212
Mouse model for the treatment of immune pregnancy loss
Toder V.; Strassburger D.; Carp H.; Irlin I.
Department of Embryology, Tel-Aviv University, Medical School,Ramat-Aviv 69978 Israel
American Journal of Reproductive Immunology ( AM. J. REPROD. IMMUNOL. ) ( Denmark) 1991, 26/1 (42-46)
CODEN: AAJID ISSN: 8755-8920
DOCUMENT TYPE: Journal; Conference Paper
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH

Spontaneous abortions can be associated with preimplantation embryo loss, implantation problems and a variety of postimplantation pregnancy failures. The long list of possible causes for the postimplantation pregnancy loss includes, among others, genetic abnormalities in fetus, anatomical abnormalities of the uterus, endocrinological insufficiency, and microbiological problems. However, more than 50% of recurrent miscarriages still have no recognized causes. The concept that many such abortions may

be immunologically mediated has gained increasing support over the years. Moreover, immunization of such women with husband's or third party leukocytes has resulted in more than 70% of subsequent pregnancies resulting in live births. Since neither the mechanisms leading to pregnancy loss nor the success of immunotherapy are clear, the set-up of animal models for recurrent abortions would be of supreme significance. Our recent data show that immunopotentiation of maternal immune system by Complete Freund Adjuvant significantly improves pregnancy rate in CBA x DBA/2 mouse combination with high percentage of fetal resorptions. This effect is followed by decrease of IL 2 production in spleen; increase of MAC 1-positive cells at placenta; amplification of suppressive activity of local and systemic lymphocytes and by reverse of embryotoxic effect of maternal serum. Data obtained in this model seems to be valuable in substantiation of rationale for nonspecific immunotherapy of human abortions.

((((((((((((((((((((((((((((((((((((((((((((((((((((((((((((((

11/7/17 (Item 13 from file: 73)
DIALOG(R)File 73:EMBASE


05508861 EMBASE No: 1993276960
Expression of cytokines in placentas of mice undergoing immunologically mediated spontaneous fetal resorptions
Tangri S.; Raghupathy R.
Immunogenetics Laboratory, National Institute of Immunology, Aruna Asaf Ali Marg,New Delhi 110067 India
Biology of Reproduction ( BIOL. REPROD. ) (United States) 1993, 49/4 (850-856)
CODEN: BIREB ISSN: 0006-3363
DOCUMENT TYPE: Journal; Article
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH

It is clear that the immune system and the reproductive system interact with and influence each other and that the immune system can have positive and negative regulatory effects on the outcome of pregnancy. The discovery of murine models of immunologically mediated spontaneous fetal resorptions has proved to be very useful for the study of immunological influences on pregnancy. In an attempt to elucidate the mechanisms underlying pregnancy impairment in one such 'natural' model of pregnancy loss, we compared the expression of the cytokines tumor necrosis factor alpha, interferon tau, and interleukin-2 in placental tissue from a resorption-prone strain combination with the expression from a normal combination. We found significantly enhanced expression of these three cytokines in placentas from the resorption-prone combination using dot-blot hybridization and Northern hybridizations. Since these cytokines are abortifacients in vivo and have detrimental effects on the placenta, and hence on fetal development and survival, our demonstration of enhanced expression of these deleterious cytokines may give insight into the mechanisms involved in immunologically mediated spontaneous abortions.

((((((((((((((((((((((((((((((\\

10232765 BIOSIS NO.: 199698687683
Immunological prevention of spontaneous early embryo resorption is mediated by non-specific immunostimulation.
AUTHOR: Baines Malcom G(a); Duclos Alain J; De Fougerolles Antonin R; Gendron Robert L
AUTHOR ADDRESS: (a)Dep. Microbiol. Immunol., McGill Univ., 3775 University St., Montreal, PQ H3A-2B4**Canada
JOURNAL: American Journal of Reproductive Immunology 35 (1):p34-42 1996
ISSN: 1046-7408
DOCUMENT TYPE: Article

RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: PROBLEM: Spontaneous early embryo resorption following implantation occurs in many species, but little is known regarding the causes or the prevention of early pregnancy failure. Embryo and fetal loss have widely been assumed to be due to maternal allospecific immune rejection. Alloimmunization therapy with paternal tissues has been successfully used in human and murine pregnancies to prevent early embryo demise. The mechanisms of this treatment have been assumed to be the induction of antigen specific, fetal "graft" enhancing antibodies and suppressor cells. The purpose of this study was to investigate the validity of this assumption. METHOD: To investigate these general assumptions, female CBA/J mice were immunized with either specific or nonspecific antigens prior to mating with DBA/2 or Balb/c males. Further, a model system for the study of bacterial lipopolysaccharide (LPS) induced abortion was used to demonstrate the nature of antigen specific immune protection against abortion. RESULTS: Whereas the administration of 1 mu-g of LPS to CFW female times CFW male pregnant mice on day 7 of gestation induced complete fetal resorption, prior immunization with 20 mu-g of LPS completely prevented LPS induced abortion as long as the anti-LPS antibody titers remained above a threshold value of about 1/500. Therefore, early embryo loss could be induced by a bacterial infection and could be prevented by appropriate immunity to abortogenic factors. However, due to the short half-life of IgM antibodies, immunity to LPS was short-lived and the protective effect of LPS immunization against LPS induced abortion waned after 5 wk. Through the use of the CBA/J female times DBA/2 male model system to study spontaneous early embryo loss, previous vaccination of CBA/J female mice with Balb/c spleen cells expressing paternal MHC antigens, complete Freund's adjuvant (CFA) or LPS, all decreased the incidence of spontaneous resorption in subsequent pregnancies. Similarly, a previous mating with a Balb/c male prevented spontaneous embryo loss for a period of up to 6 wk. However, none of the immunotherapeutic vaccinations or matings had a permanent effect on CBA/J female times DBA/2 male embryo survival, which one would have expected if specific immune mediators were involved. CONCLUSION: The results of this study indicated that the decrease in the incidence of spontaneous embryo resorption following alloimmunization was more likely to be due to nonspecific immunomodulatory effects on the immune system of the female mice, as opposed to specific antipaternal immunity. This may, in part, explain the placebo effects observed for alloimmunization therapy for human habitual pregnancy loss. The relevance of these results to the development of immunotherapy strategies for the prevention of habitual abortion is discussed.

((((((((((((((((((((((((((())))))))))))))))))))))))))) probably already have requested just wanted to give you the last hit references ))))))))))))))))))

| Set | Items | Description |
|---|---|---|
| S1 | 707 | (SPONTANEOUS(W)ABORTION) AND MODEL? |
| S2 | 590 | S1 AND HUMAN? |
| S3 | 109 | S2 AND (CORRELAT? OR PREDICT?) |
| S4 | 72 | RD S3 (unique items) |
| S5 | 4 | S4 AND (DBA?) |
| S6 | 4 | RD S5 (unique items) |
| S7 | 0 | (SPONTANEOUS(W)ABORTION)(20N)(MURINE OR MOUSE) AND (CORRELAT? OR PREDICT?)(10N)(HUMAN) |
| S8 | 7 | (SPONTANEOUS(W)ABORTION)(20N)(MURINE OR MOUSE) AND (CORRELAT? OR PREDICT?) AND (HUMAN) |
| S9 | 5 | RD S8 (unique items) |
| S10 | 22 | (SPONTANEOUS(W)ABORTION)(20N)(MURINE OR MOUSE) AND (MODEL?) |

AND (HUMAN)
S11 20 RD S10 (unique items)
S12 12 SPONTANEOUS(W)ABORTION AND MISCARRIAGE AND DBA?
S13 6 RD S12 (unique items)
S14 117 SPONTANEOUS(W)ABORTION AND DBA?
S15 58 RD S14 (unique items)
S16 19 S15 AND HUMAN?
? t s16/7/all

16/7/1 (Item 1 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)


13720761 BIOSIS NO.: 200200349582
Thinking outside the box: Mechanisms of environmental selective pressures on the outcome of the materno-fetal relationship.
AUTHOR: Clark David A(a); Chaouat Gerard; Gorczynski Reginald M
AUTHOR ADDRESS: (a)Departments of Medicine, Molecular Medicine and Pathology, Obstetrics and Gynecology, McMaster University, 1200 Main Street West, Rm 3V39, Hamilton, Ontario, L8N 3Z5**Canada E-Mail: clarkd@mcmaster.ca
JOURNAL: American Journal of Reproductive Immunology 47 (5):p275-282 May, 2002
MEDIUM: print
ISSN: 1046-7408
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: PROBLEM: Study of mechanisms causing spontaneous abortion of the vascularized placenta have focused primarily on the feto-maternal immunological relationship within the pregnant mother. The Th1 cytokines such as tumor necrosis factor (TNF)-alpha + interferon (IFN)-gamma derived in part from natural killer (NK) and NKgammadeltaT cells have been implicated in causing abortion via up-regulation of the novel prothrombinase fg12 at the feto-maternal interface; Th2/3 cytokines such as interleukin (IL)-10, progesterone-induced blocking factor (PIBF), and TGF-beta2 derived from gammadeltaT cells stimulated by embryo antigens in the context of the OX-2 (CD200) tolerance signal have been viewed as counteracting the Th1 effect. These mechanisms are distinct from those causing and preventing occult pregnancy loss during the periimplantation phase of pregnancy prior to development of a vascularized placenta. Spontaneous abortions in the CBA/J X DBA/2 can be boosted by injecting TNF-alpha + IFN-gamma, but the boosted abortion rates can range from Itoreq 30 to > 80%, depending on the loss rate in uninjected mice, and this is not explainable by the endogenous level of these cytokines. Furthermore, there is a poor correlation between Th1/Th2,3 cytokine ratios and abortion rates. Could there be a third factor involved, and if so, what might this mean? METHODS: Known precipitants of recurrent abortion in mice were reviewed with particular attention to stress and endotoxin absorption. The effect of antagonizing the response to bacterial lipopolysaccharide (LPS) (endotoxin) was tested. Data on environmental selective pressures were considered (i.e. thinking outside the 'box', which typifies the conventional approach to thinking about materno-fetal interactions). RESULTS: Th1 cytokine-triggered abortions appear to depend on availability/presence of LPS. CONCLUSIONS: Environmental selective pressures are implicated in eliminating 'genetically weaker' embryos in early pregnancy.

16/7/2 (Item 2 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

13358211 BIOSIS NO.: 200100565
Biological activity of the suppressor cells inducer factor secreted by the Jeg-3 choriocarcinoma cell line.
AUTHOR: Markert U R(a); Chaouat G
AUTHOR ADDRESS: (a)Abteilung fuer Geburtshilfe, Friedrich-Schiller-Universitaet, 07740, Jena: udo.markert@med.uni-jena.de **Germany
JOURNAL: American Journal of Reproductive Immunology 46 (5):p332-341 November, 2001
MEDIUM: print
ISSN: 1046-7408
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English
SUMMARY LANGUAGE: English

ABSTRACT: PROBLEM: We wanted to further study the mechanisms of immune suppression and suppression inducing capacities by choriocarcinoma products, e.g. both crude human choriocarcinoma supernatant (HCS) and especially an active fraction obtained by high performance liquid chromatography (HPLC) from the culture supernatant of the Jeg-3 human choriocarcinoma cell line, since it appeared by weight and charge criteria to be a different molecular species than the low molecular weight fraction previously isolated from mouse and human term placenta. It was important to know whether the purified material was active in vivo as it was in vitro. Therefore, we tested the effects of HCS in vivo in three systems: prevention of fetal demise in the CBA/JXDBA/2 abortion prone murine mating combination, where the effects of the HPLC purified fraction were also monitored as well as by a cell transfer system, where the suppression is revealed by a local GVH/HVG assay, and finally enhancement the survival of a mildly immunogenic tumor allograft. METHODS: An active fraction was isolated from HCS by ion exchange HPLC. Female CBA/J were mated with DBA/2 and the influence of 3 intraperitoneal injections of both crude HCS and the active fraction was evaluated by monitoring the percentage of fetal resorptions. Simultaneously, on the day when resorptions were counted, maternal splenocytes from these females were harvested and were injected by the subcutaneous way in C3H/HEJ hind feet. The lymph node reactivity (HVG+GVH) was assessed by (3H)thymidine intake by cells harvested from the draining popliteal lymph nodes. For assessment of influence of HCS on allograft rejection, BALB/b (H-2b) mice received a subcutaneous injection of allogeneic P815 tumor cells (H-2d). The influence of HCS injections on tumor survival was analyzed by regular measurements of the mean tumor diameter. RESULTS: Intraperitoneal injection of HCS reduced fetal resorptions from 24.7 to 13%. Injection of the in vitro active fraction induced the same rate of reduction. The mean intensity of HvG/GvH reaction was 13400 cpm per lymph node when splenocytes from the control group were injected compared to 2900 cpm when splenocytes from treated mice were used. P815 tumor allografts were completely rejected in all cases after 21 days. Weekly subcutaneous injections of HCS prolonged tumor survival in all cases up to at least 30 days. CONCLUSION: The fraction isolated from HCS increased very efficiently the survival of allografts as well as those of allogeneic fetuses in a resorption prone murine mating. The choriocarcinoma cell line might prove to be a useful source of immunosuppressive materials, which could otherwise be important for the fetal-maternal tolerance and a successful pregnancy.

16/7/3 (Item 3 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)


13269043 BIOSIS NO.: 200100476192
Activation of the novel prothrombinase, fgl2, as a basis for the pregnancy

complications spontaneous abortion and pre-eclampsia.
AUTHOR: Knackstedt M(a); Ding J W(a); Arck P C; Hertwig K; Coulam C B; August C; Lea R; Dudenhausen J W; Gorczynski R M(a); Levy G A(a); Clark D A(a)
AUTHOR ADDRESS: (a)Toronto General Hospital Research Institute, University of Toronto, Toronto, Ontario**Canada
JOURNAL: American Journal of Reproductive Immunology 46 (3):p196-210 September, 2001
MEDIUM: print
ISSN: 1046-7408
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English
SUMMARY LANGUAGE: English

ABSTRACT: PROBLEM: Impaired trophoblast invasion during the first trimester of pregnancy is linked to spontaneous abortion, and defective invasion in the second trimester to hypertension + proteinuria (pre-eclampsia). Hypertension developing during the third trimester of human pregnancy represents, in part, a corrective response in the mother to provide adequate placental perfusion for fetal growth when trophoblast has not to invaded and converted the myometrial proportion of maternal spiral arteries into to low resistance-high capacitance conduits. Deportation of vesicles from hypoxemic trophoblast is thought to cause hypertension plus proteinuria, vascular damage and a systemic coagulopathy. Trophoblast invasion may be inhibited by local cytokines, such as TGF-betas but Th1-type cytokines associated with pre-eclampsia and spontaneous abortions (e.g., IL-1, TNF-alpha, IFN-gamma) are not known to inhibit migration at in situ concentrations. Trophoblast invasion is also inhibited by the binding of surface integrins to fibronectin and fibrin, and fibrin production is stimulated by these Th1 cytokines via up-regulation of prothrombinases(s) such as fgl2 which directly and via TNF-alpha-facilitated inflammation compromise trophoblast cell integrity. We, therefore, asked if fgl2 expression and TNF-alpha are increased in first trimester human miscarriage and in third trimester pre-eclampsia. METHODS: fgl2 mRNA was detected using in situ hybridization and fgl2 protein by immunohistochemistry. TNF-alpha mRNA and protein were similarly tested. The techniques were validated using uterine sections from day 8.5 of CBA X DBA/2 pregnancies, and then were applied to sections of placentae from normal and pre-eclamptic pregnancies with and without intrauterine fetal growth restriction (IUGR). Fibrin was detected by immunohistochemistry. RESULTS: Expression of fgl2 protein correlated with fgl2 mRNA expression in mouse uteri and in placentae from normal human pregnancies. Increased expression of fgl2 and TNF-alpha mRNA and protein, and increased fibrin deposition was detected in placental trophoblast. CONCLUSIONS: Activation of fgl2 prothrombinase by Th1-type cytokines in pregnancy may lead to spontaneous abortion, or in ongoing pregnancy, to pre-eclampsia and/or IUGR.

16/7/4 (Item 4 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)


12132198 BIOSIS NO.: 199900427047
The emerging role of immunoregulation of fibrinogen-related procoagulant fgl2 in the success or spontaneous abortion of early pregnancy in mice and humans.
AUTHOR: Clark David A(a); Ding Jin-Wen; Chaouat Gerard; Coulam Carolyn B; August Carey; Levy Gary A
AUTHOR ADDRESS: (a)Departments of Medicine, Pathology, Obstetrics, and Gynecology, McMaster University, 1200 Main St. West, Rm 3V39, Hamilton, ON, L8N 3Z5**Canada

JOURNAL: American Journal of Reproductive Immunology 42 (1):p37-43 July, 1999
ISSN: 1046-7408
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English
SUMMARY LANGUAGE: English

ABSTRACT: PROBLEM: Abortion of chromosomally normal embryos in the CBA X DBA/2 mating combination is triggered by release of Th1 cytokines (tumor necrosis factor (TNF)-alpha, interferon (IFN)-gamma, and interleukin (IL)-1), which cause abortion via a novel prothrombinase, fgl2, and polymorphonuclear leukocytes. The site of activation may be maternal vascular endothelium on arteries and veins nourishing the placenta. Activation of coagulation is also prominent in spontaneous abortion of chromosomally normal human embryos. We asked where is fgl2 up-regulated in the uterus in murine abortions, and if similar fgl2 expression occurs in human pregnancy failure. METHODS: Control CBA X DBA/2 pregnant mice, or from mice injected with TNF-alpha + IFN-gamma on day 7.5 of gestation, were removed on day 8.5, fixed, sectioned, and subject to in situ hybridization for fgl2. Sections were also stained for fibrin. Elective first trimester termination samples or biopsies taken early in the course of a recurrent miscarriage were similarly fixed, sectioned, and analyzed by in situ hybridization. Control and cytokine-treated mice were anticoagulated with heparin, an activator of antithrombin III, and/or the direct anti-thrombin inhibitor hirudin. RESULTS: Low level fgl2 expression localized to basal decidua remote from the embryo was noted in control mice; cytokine treatment, which causes greater than 80% of abortions, produced a striking up-regulation in this area as well as in a band at the junction of decidua and myometrium. Trophoblast also became strikingly positive. Fgl2 expression was associated with increased fibrin staining. Anticoagulation significantly protected against abortions, but doses were limited by the complication of retroplacental hemorrhage. In tissue from normal first trimester pregnancy, minimal fgl2 positivity was seen in some villous syncytiotrophoblast, in villous stroma, cytotrophoblast, and in some cells in decidua. In spontaneous abortion of normal embryo, striking fgl2 positivity was seen in syncytiotrophoblast and extravillous cytotrophoblast, in association with areas of thrombus formation. CONCLUSIONS: Fgl2 appears to be physiologically expressed and may protect against the internal danger of maternal and/or fetal bleeding during pregnancy and at parturition; a role in inhibiting transplacental traffic is also possible. External dangers in the form of stress, endotoxin, and antigens eliciting Th1 cytokine responses upregulate fgl2 prothrombinase in trophoblast as well as in decidua, which results in spontaneous abortion of immunogenetically "weaker" embryos.

16/7/5 (Item 5 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)


11044505 BIOSIS NO.: 199799665650
Maternal response to paternal trophoblast antigens.
AUTHOR: Mowbray James(a); Jalali Reza; Chaouat Gerard; Clark David A; Underwood Jennifer; Allen W R; Mathias Susanna
AUTHOR ADDRESS: (a)Imperial Coll. Sch. Med. at St. Mary's, London W2**UK
JOURNAL: American Journal of Reproductive Immunology 37 (6):p421-426 1997
ISSN: 1046-7408
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: PROBLEM: What is the function of the immunoglobulin (Ig) G

antibody bound to trophoblast in normal pregnancy, and what is the antigen? METHOD: IgG was acid eluted from term human placental microvesicles and reacted with the antigen, R80K, left on the vesicles. The eluted antibody was used to detect the antigen on monocytes, lymphocytes, and lymphoblastoid cell lines. The eluted antibody is highly polymorphic, but monoclonal antibodies (mAbs) were made against conserved regions of the molecule. These also reacted with the murine equivalent of the human R80K and were used in inhibition studies of natural killer (NK) cell killing and the mouse abortion models, CBA times DBA2 F1 resorption in CBA females, the endotoxin-induced resorption model, and a sonic stress-induced murine resorption model. RESULTS: All 600 syncytiotrophoblast microvesicle preparations of human term placenta had IgG antibody bound, elutable at pH 3.0. The eluted antibody reacted with about 15% of unrelated human placentae. In horses mares make detectable antibody early in pregnancy, at about the time of implantation. The IgG antibody was bound to an 80-kDa protein (R80K) also detected on B lymphocytes and monocytes. In HLA homozygous lymphoblastoid B cell lines, which reacted with one or more eluted antibodies, had a pattern of cytotoxicity independent of HLA Class I; and as a single 80-kDa peptide chain, R80K did not resemble HLA molecules. Genetic studies in horses show that of the two paternal allotypes of R80K detectable by placental alloantibodies, only one, usually the grandpaternal one, is present in all the placentae of a sibship. Two of 26 eluted human antibodies had affinity for K562 and inhibited killing by human peripheral blood NK cells. One mAb, BA11, against a conserved site on R80K inhibited killing of K562, and also reacted with the murine R80K homologue. BA11 inhibited murine NK cell killing and virtually completely inhibited three NK cell-dependent mouse resorption models. CONCLUSION: R80K protein is a target molecule for NK cell activity expressed on all placentae. It has a polymorphic alloantigenic determinant completely covered with maternal antibody in all successful term pregnancies. In murine NK cell-dependent models of abortion, a mAb against a monomorphic determinant present in human and murine R80K prevents abortion very effectively. It seems that the R80K molecule must be covered with antibody to prevent NK attacks on trophoblast.

16/7/6 (Item 6 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)


10488598 BIOSIS NO.: 199699109743
Immunoactive products of placenta. V. Immunoregulatory properties of a low molecular weight compound obtained from human placental cultures.
AUTHOR: Djian Valentine; Menu Elisabeth; Thibault Gilles; Ropert Sylvie; Chaouat Gerard(a)
AUTHOR ADDRESS: (a)Batiment de Gynecologie/Obstetrique, Universite Paris Sud/Assistance Publique, Hopital Antoine B**France
JOURNAL: American Journal of Reproductive Immunology 36 (1):p11-24 1996
ISSN: 1046-7408
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: PROBLEM: We have previously shown that supernatants from short-term cultures of human placental explants (HPS) are immunosuppressive in vitro as well as in vivo. They contain a low M.W. factor endowed with immunoregulatories activities (Filtrate of such with a 5 kDa cut off). In this paper, we wanted to assess whether this low M.W. material accounts for most, if not all, of the immunosuppressive properties of crude HPS and begin to investigate its mode of action. RESULTS: The filtrate is active across species barrier and inhibits human and murine PHA driven lymphocyte proliferation, Mixed Lymphocyte Reaction, and Natural Killer activity as did crude HPS. It

does not affect CTL lytic function at effector stage. Its cross species activity allowed us to study its effects in vivo. It corrects resorbtions in the CBA times DBA/2 murine spontaneous abortion model, and suppresses local and general GVH reactions in a model (A cells into irradiated A times B FIs) relevant to a clinical use, e.g., bone marrow transplantation. To ensure that such survival of the recipients was due to donor cells in the latter, surviving experimental animals were analysed by FACS for repopulating lymphocytes phenotype, which was indeed of donor origin. To elucidate the mechanisms of action of the active HPS moiety, we first tested various malignant cell lines for the minimal incubation time required for maximal lymphocyte inhibition. In the same vein, we verified that lymphocytes stimulated by PHA and simultaneously treated with filtrate were unresponsive to a second PHA challenge. The effects of the material was reversible if cells were washed out of it early enough before otherwise entering a cycle leading ultimately to cell death in vitro. Finally, we tested several second messenger pathways, none of which were modified. CONCLUSION: These data suggest that the filtrate contains an entity that represents the main, if not all, the immunosuppressive molecules present in HPS. In addition, they suggest that the material acts only on activated T cells and requires to be present early in the replication activation cycle. Altogether, the in vitro data strongly suggest that the material is acting by inducing clonal deletion in activated (T) cells.

16/7/7 (Item 7 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)


10232765 BIOSIS NO.: 199698687683
Immunological prevention of spontaneous early embryo resorption is mediated by non-specific immunostimulation.
AUTHOR: Baines Malcom G(a); Duclos Alain J; De Fougerolles Antonin R; Gendron Robert L
AUTHOR ADDRESS: (a)Dep. Microbiol. Immunol., McGill Univ., 3775 University St., Montreal, PQ H3A-2B4**Canada
JOURNAL: American Journal of Reproductive Immunology 35 (1):p34-42 1996
ISSN: 1046-7408
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: PROBLEM: Spontaneous early embryo resorption following implantation occurs in many species, but little is known regarding the causes or the prevention of early pregnancy failure. Embryo and fetal loss have widely been assumed to be due to maternal allospecific immune rejection. Alloimmunization therapy with paternal tissues has been successfully used in human and murine pregnancies to prevent early embryo demise. The mechanisms of this treatment have been assumed to be the induction of antigen specific, fetal "graft" enhancing antibodies and suppressor cells. The purpose of this study was to investigate the validity of this assumption. METHOD: To investigate these general assumptions, female CBA/J mice were immunized with either specific or nonspecific antigens prior to mating with DBA/2 or Balb/c males. Further, a model system for the study of bacterial lipopolysaccharide (LPS) induced abortion was used to demonstrate the nature of antigen specific immune protection against abortion. RESULTS: Whereas the administration of 1 mu-g of LPS to CFW female times CFW male pregnant mice on day 7 of gestation induced complete fetal resorption, prior immunization with 20 mu-g of LPS completely prevented LPS induced abortion as long as the anti-LPS antibody titers remained above a threshold value of about 1/500. Therefore, early embryo loss could be induced by a bacterial infection and could be prevented by appropriate immunity to abortogenic factors. However, due to the short half-life of

IgM antibodies, immunity to LPS was short-lived and the protective effect of LPS immunization against LPS induced abortion waned after 5 wk. Through the use of the CBA/J female times DBA/2 male model system to study spontaneous early embryo loss, previous vaccination of CBA/J female mice with Balb/c spleen cells expressing paternal MHC antigens, complete Freund's adjuvant (CFA) or LPS, all decreased the incidence of spontaneous resorption in subsequent pregnancies. Similarly, a previous mating with a Balb/c male prevented spontaneous embryo loss for a period of up to 6 wk. However, none of the immunotherapeutic vaccinations or matings had a permanent effect on CBA/J female times DBA/2 male embryo survival, which one would have expected if specific immune mediators were involved. CONCLUSION: The results of this study indicated that the decrease in the incidence of spontaneous embryo resorption following alloimmunization was more likely to be due to nonspecific immunomodulatory effects on the immune system of the female mice, as opposed to specific antipaternal immunity. This may, in part, explain the placebo effects observed for alloimmunization therapy for human habitual pregnancy loss. The relevance of these results to the development of immunotherapy strategies for the prevention of habitual abortion is discussed.

16/7/8 (Item 8 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)


09831337 BIOSIS NO.: 199598286255
In Vivo Immunosuppressive Effects of Recombinant Ovine Interferon-tau (Trophoblastin): r.oTP (r.oIFN-tau) Inhibits Local GVH Reaction in Mice (PLN Assay), Prevents Fetal Resorptions, and Favors Embryo Survival and Implantation in the CBA/J x DBA/2 Mice Combination.
AUTHOR: Assal-Meliani Aines(a); Kinsky Radoslav; Martal Jacques; Chaouat Gerard
AUTHOR ADDRESS: (a)CJF Inserm 92-09 Biol. Cell. Mol., Relation Materno Foetale, Batiment Gynecol. Obstet., Hop. Ant**France
JOURNAL: American Journal of Reproductive Immunology 33 (3):p267-275 1995
ISSN: 1046-7408
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: PROBLEM: Ovine trophoblastin protein, be it natural or recombinant (o.TP, r.oTP), a member of the tau interferon family (r.oIFN-tau), has been shown to possess immunosuppressive properties in vitro. It acts as a cytostatic agent across species. Indeed, it was immunosuppressive when tested on human and murine lymphocytes in a variety of in vitro immune assays, as it is also on syngenic (ovine) lymphocytes. METHODS: In the present paper, we first verified that this property to act across species also occurred in vivo assays; roTP was able to down regulate a local GVH reaction assay (PLN assay) in mice. We then took advantage of these properties of r.oTP to investigate its in vivo effects during murine pregnancy as there is no ovine equivalent of the murine CBA/ J times DBA/2 resorption prone mating combination. RESULTS: When given in the postimplantation period, r.oTP drastically boosted resorptions in the CBA/J times DBA/2 matings, as did murine recombinant gamma interferon. However, the same roTP treatment in the peri-implantation period resulted in a reduction in resorptions in this spontaneous abortion system. CONCLUSION: The data suggested that roTP might have acted more by favouring implantation and embryo survival than by preventing the resorption process itself. The mechanisms possibly underlying these effects, as well as the putative uses of r.oTP evolving from these data, are discussed.

16/7/9 (Item 9 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)


08967362 BIOSIS NO.: 199396118863
Murine trophoblast failure and spontaneous abortion.
AUTHOR: Clark David A(a); Banwatt Daljeet; Croy B Anne
AUTHOR ADDRESS: (a)Molecular Virology-Immunology Program, McMaster Univ., 1200 Main Street West, Room 3V39, Hamilto**Canada
JOURNAL: American Journal of Reproductive Immunology 29 (4):p199-205 1993
ISSN: 1046-7408
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Problem: Infection has been proposed to initiate abortion, and the role of viruses in spontaneous resorption in mice has not been tested. Methods: The anti-viral drug ribavirin (1-beta-D-ribofuranosyl-1,2,4-triazole-3-carboxamide) was fed to CBA/J and C3H/HeJ female mice beginning on the morning after mating with DBA/2J males. Results: Ribavirin treatment increased the rate of abortion (resorption) on day 13.5, and this was associated with retardation of the rate of embryo development and hypoplasia of the trophoblast. There was a reduction in trophoblast-dependent decidua-associated soluble suppressor activity, but there was no maternal mononuclear cell infiltrate of the type reported in association with resorption of semiallogeneic and xenogeneic mouse embryos. This may be due to an immunosuppressive effect of ribavirin. Ribavirin was able to potently suppress proliferation of mouse trophoblast and mastocytoma cell lines in vitro. Conclusions: There are several drug-induced murine abortion models that provide useful insights into potential mechanisms underlying spontaneous pregnancy failure, but in the ribavirin model, a direct impairment of trophoblast development appears to be responsible.

16/7/10 (Item 10 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)


08948198 BIOSIS NO.: 199396099699
Stress-triggered abortion in mice prevented by alloimmunization.
AUTHOR: Clark David A(a); Banwatt Daljeet; Chaouat Gerard
AUTHOR ADDRESS: (a)Rm 3V39, McMaster Univ., 1200 Main St. West, Hamilton, Ontario, Can. L8N 3Z5
JOURNAL: American Journal of Reproductive Immunology 29 (3):p141-147 1993
ISSN: 1046-7408
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: PROBLEM: To determine if immunotherapy can prevent abortion triggered by mechanisms that in humans may be treatable by psychotherapy. METHOD: The effects of alloimmunization against paternal strain antigens were tested in pregnant mice subjected to stress. RESULTS: Restraint stress boosted the resorption rate assessed on day 13.5 of pregnancy in DBA/2-mated C3H/HeJ mice with optimal effect on day 4.5 of pregnancy, and premating alloimmunization greatly reduced the effect. By contrast CBA/J and A/J mice proved resistant to abortion boosting by restraint stress. A/J mice mated to DBA/2 or C3H/HeJ males showed reduced fertility, perhaps due to failure of pregnancy immediately after the stress, but this was not corrected by alloimmunization with either DBA/2 (class I + class II major histocompatibility complex (MHC) immunogen) or C3H/HeJ (class I MHC immunogen) splenocytes. There was a reduction in the endogenous

resorption rate, however, and implantation number was slightly increased by preimmunization using DBA/2 cells. The abortion rate could be boosted, however, by ultrasonic noise stress of high abortion rate CBA/J, and preimmunization using BALB/c (H-2-d) splenocytes protected. A similar boosting of loss in low abortion rate BALB/k mice was ameliorated (albeit not completely) by preimmunization with allogeneic paternal but not syngeneic splenocytes. CONCLUSIONS: Immunotherapy may protect against a variety of potential triggers of spontaneous abortion, including those that may be amenable to psychological remedies, and possible mechanisms are discussed.

16/7/11 (Item 11 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)


08917021 BIOSIS NO.: 199396068522
Effect of prostaglandin synthesis inhibitors on spontaneous and endotoxin-induced abortion in mice.
AUTHOR: Clark David A; Banwatt Daljeet; Chaouat Gerard
AUTHOR ADDRESS: Rm 3V39 McMaster Univ., 1200 Main Street West, Hamilton, Ontario L8N 3Z5**Canada
JOURNAL: Journal of Reproductive Immunology 24 (1):p29-44 1993
ISSN: 0165-0378
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: The putative role of prostaglandin E-2 (PGE-2) in suppressing rejection of the 'fetal allograft' (resorption) in C3H/HeJ and CBA/J allopregnant mice was tested by administration of the prostaglandin synthesis inhibitors indomethacin (INDO) and acetylsalicylic acid (ASA). When the resorption rate was low, INDO fed at a dose of 15 mu-g/ml in drinking water after implantation had a slight augmenting effect when the endogenous resorption rate was lt 30%, but had no effect when the endogenous rate was higher or when bacterial lipopolysaccharide (LPS) was given. ASA fed at 50 mu-g/ml had no augmenting effect and did not increase sensitivity to the abortogen LPS in either CBA/J (LPS sensitive) or C3H/HeJ (LPS resistant) mice. Both INDO and ASA fed to CBA/J mice significantly reduced endogenous PGE-2 extractable from the uteri of hormonally pseudopregnant mice after deciduoma induction. Feeding INDO at doses up to 30 mu-g/ml from day 2.5 of pregnancy impaired but failed to completely block implantation in CBA/J mice, and with daily administration, some of the mice became sick: all of the implants in sick mice resorbed. INDO at doses of 150-200 mu-g per day known to inhibit implanatation in vivo by sufficiently blocking PGE-2 synthesis, was injected on one or more days beginning after the time of implantation. This failed to cause abortion in CBA/J mice and although some mice became ill, provided this happened after day 8.5 of pregnancy when sensitivity to the abortogenic effects of injected LPS decreased substantially in these mice, all implants in the sick mice were 'healthy' (i.e. non-resorbing). We were unable to increase the rate of resorption in syngeneically pregnant CD1 mice above 13% with 15 ml INDO in drinking water. Our data do not support the view that PGE-2 represent an important intrauterine suppressor molecule blocking the processes mediating embryo death at the time of abortion. Spontaneous abortion in DBA/2-mated CBA/J mice appears to be determined by the level of bacterial LPS (endotoxin) and treatment with antibiotics or intralipid (which enhances endotoxin clerance), reduces the abortion rate. A sufficent dose of INDO many cause abortion, but the data taken together suggest this may be due to effects on the gut whereby permeability to bacterial LPS is increased.

16/7/12 (Item 12 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)


07205097 BIOSIS NO.: 000039119451
INFLUENCE OF TREATMENT WITH MOUSE IMMUNOGLOBULIN ON THE RATE OF VIABLE NEONATES IN THE CBA-J X DBA-2J MODEL
AUTHOR: HEINE O; MUELLER-ECKHARDT G; PABST W
AUTHOR ADDRESS: DEP. GYNECOL. AND OBSTETRICS, JUSTUS LIEBIG UNIV., D-6300 GIESSEN, FRG.
JOURNAL: TENTH ANNIVERSARY MEETING OF THE AMERICAN SOCIETY FOR THE IMMUNOLOGY OF REPRODUCTION, CHICAGO, ILLINOIS, USA, JUNE 20-23, 1990. AM J REPROD IMMUNOL 22 (3-4). 1990. 74-75. 1990
CODEN: AJRIE
DOCUMENT TYPE: Meeting
RECORD TYPE: Citation
LANGUAGE: ENGLISH

16/7/13 (Item 13 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)


05718580 BIOSIS NO.: 000084066986
ALLOGENEIC MATINGS AND IMMUNIZATION HAVE DIFFERENT EFFECTS ON NULLIPAROUS AND MULTIPAROUS MICE
AUTHOR: CHAVEZ D J; MCINTYRE J A; COLLIVER J A; FAULK W P
AUTHOR ADDRESS: METHODIST CENT. REPRODUCTION TRANSPLANTATION IMMUNOL., 1701 N. SENATE BLVD., INDIANAPOLIS, IN 46202.
JOURNAL: J IMMUNOL 139 (1). 1987. 85-88. 1987
FULL JOURNAL NAME: Journal of Immunology
CODEN: JOIMA
RECORD TYPE: Abstract
LANGUAGE: ENGLISH

ABSTRACT: CBA/J female mice have a high rate of spontaneous fetal loss when mated with DBA/2 males. We have confirmed that this fetal resorption rate can be significantly reduced by immunizing the female with C57BL rather than DBA leukocytes. The current studies have been extended to show the effect of continued immunization into second pregnancies. Three new findings emerge: a) second pregnancies in unimmunized CBA/J females .times. DBA/2 males proceed with a low percentage of spontaneous resorptions; b) continued immunization of multigravid, multiparous mice is associated with a high percentage of late onset fetal resorptions; and c) comparison of sex ratios between treated and untreated pregnancies showed no significant shift. These results suggest that untreated CBA/J females mated to DBA/2 males can be immunized to trophoblast antigens during first pregnancies, and that such immunization leads to "normal" reproductive outcome in subsequent untreated pregnancies. Persistent immunizaton with leukocytes appears to increase the percentage of fetal wastage in subsequent pregnancies regardless of whether the mother receives paternal or nonpaternal leukocytes. Intentional chronic immunization with male leukocytes does not influence the sex ratio of viable offspring. These data are discussed with reference to immunotherapy for women who suffer unexplained, recurrent spontaneous abortions.

16/7/14 (Item 1 from file: 73)
DIALOG(R)File 73:EMBASE


11017198 EMBASE No: 2001064410
Fgl2 prothrombinase expression in mouse trophoblast and decidua triggers

abortion but may be countered by OX
Clark D.A.; Ding J.-W.; Yu G.; Levy G.A.; Gorczynski R.M.
D.A. Clark, Dept. of Med., Pathol./Molec. Med., Dept. of Obstetrics and Gynecology, McMaster University, 1200 Main St West, Hamilton, Ont. L8N 3Z5 Canada
AUTHOR EMAIL: clarkd@fhs.McMaster.ca
Molecular Human Reproduction ( MOL. HUM. REPROD. ) (United Kingdom) 2001, 7/2 (185-194)
CODEN: MHREF ISSN: 1360-9947
DOCUMENT TYPE: Journal ; Article
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH
NUMBER OF REFERENCES: 49

Spontaneous abortion of normal karyotype embryos in mice and in humans is associated with an increase in uterine T helper (Th) 1 type proinflammatory cytokines, tumour necrosis factor (TNF)-alpha, interferon-gamma and interleukin (IL)-1, and a deficiency of Th2/3 type cytokines, IL-4, IL-10, and transforming growth factor (TGF)-beta2. In mice, Th1 cytokines up-regulate a novel prothrombinase, fgl2, which via thrombin, leads to activation of polymorphonuclear leukocytes that terminate the pregnancy. Here we show that Th1 cytokines up-regulate fgl2 mRNA in fetal trophoblast and secondary decidua of CBA/J x DBA/2 and CBA/J x BALB/c matings, and promote fibrin deposition. This pattern is accompanied by a high rate of abortion. However, the spontaneous abortion rates in abortion-prone CBA x DBA/2 matings and in low abortion rate CBA x BALB/c matings were significantly lower than that expected from the frequency of implantations with high levels of fibrin and fgl2 mRNASUPhi. As the glycoprotein OX-2 occurs in the pregnant rat uterus and can deviate cytokine responses to Th2/3, we investigated OX-2 in pregnant CBA/J mice. We found OX-2 mRNA was present at the same sites as fgl2 mRNA, but was reduced in response to Th1 cytokines. Furthermore, anti-OX-2 raised the abortion rate to predicted levels, while recombinant OX-2 dramatically reduced the abortion rate. Fgl2 prothrombinase may provide a mechanism explaining pregnancy loss, and conversely, successful pregnancy may be due in part to OX-2-dependent activation of maternal tolerance mechanisms at the feto-maternal interface.

16/7/15 (Item 2 from file: 73)
DIALOG(R)File 73:EMBASE


06590277 EMBASE No: 1996254935
Immunoactive products of placenta. V. Immunoregulatory properties of a low molecular weight compound obtained from human placental cultures
Djlan V.; Menu E.; Thibault G.; Ropert S.; Chaouat G.
Batiment de Gynecologie-Obstetrique, Univ. Paris Sud-Assistance Publique, Hopital Antoine Beclere, Avenue de la Forte de Trivaux,Clamart 92140 France
American Journal of Reproductive Immunology ( AM. J. REPROD. IMMUNOL. ) ( Denmark) 1996, 36/1 (11-24)
CODEN: AAJID ISSN: 8755-8920
DOCUMENT TYPE: Journal; Article
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH

PROBLEM: We have previously shown that supernatants from short-term cultures of human placental explants (HPS) are immunosuppressive in vitro as well as in vivo. They contain a low M.W. factor endowed with immunoregulatories activities (Filtrate of such with a 5 kDa cut off). In this paper, we wanted to assess whether this low M.W. material accounts for most, if not all, of the immunosuppressive properties of crude HPS and begin to investigate its mode of action. RESULTS: The filtrate is active across species barrier and inhibits human and murine PHA driven lymphocyte proliferation, Mixed Lymphocyte Reaction, and Natural Killer

activity as did crude HPS. It does not affect CTL lytic function at effector stage. Its cross species activity allowed us to study its effects in vivo. It corrects resorbtions in the CBA x DBA/2 murine spontaneous abortion model, and suppresses local and general GVH reactions in a model (A cells into irradiated A x B F1s) relevant to a clinical use, e.g., bone marrow transplantation. To ensure that such survival of the recipients was due to donor cells in the latter, surviving experimental animals were analysed by FAGS for repopulating lymphocytes phenotype, which was indeed of donor origin. To elucidate the mechanism(s) of action of the active HPS moiety, we first tested various malignant cell lines for the minimal incubation time required for maximal lymphocyte inhibition. In the same vein, we verified that lymphocytes stimulated by PHA and simultaneously treated with filtrate were unresponsive to a second PHA challenge. The effects of the material was reversible if cells were washed out of it early enough before otherwise entering a cycle leading ultimately to cell death in vitro. Finally, we tested several second messenger pathways, none of which were modified. CONCLUSION: These data suggest that the filtrate contains an entity that represents the main, if not all, the immunosuppressive molecules present in HPS. In addition, they suggest that the material acts only on activated T cells and requires to be present early in the replication activation cycle. Altogether, the in vitro data strongly suggest that the material is acting by inducing clonal deletion in activated (T) cells.

16/7/16 (Item 3 from file: 73)
DIALOG(R)File 73:EMBASE


05996715 EMBASE No: 1995025360
Intralipid as treatment for recurrent unexplained abortion?
Clark D.A.
Dept Med Pathol Obstetrics Gynecol, McMaster University, 1200 Main St West,Hamilton, Ont L8N 3Z5 Canada
American Journal of Reproductive Immunology ( AM. J. REPROD. IMMUNOL. ) ( Denmark) 1994, 32/4 (290-293)
CODEN: AAJID ISSN: 8755-8920
DOCUMENT TYPE: Journal; Article
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH

Problem: Safe, effective, and inexpensive alternatives to partner leukocyte immunotherapy are being sought. Psychotherapy may be effective but it is uncertain what constitutes effective treatment and the form of treatment tested in cohort controlled trials is expensive. IVIG also appears effective, but is expensive. Method: A published double blind randomized controlled trial in which Intralipid was used as a control versus trophoblast membrane vesicles was reviewed. A prediction made from this data was then tested using the DBA/2-mated CBA/J mouse model of recurrent spontaneous abortion. Results: It can be hypothesized from the human clinical trial data that Intralipid even in small doses could be an effective antiabortion treatment. The number of patients in the published study is too small for the required degree of precision. Intralipid was highly effective in preventing abortion in mice, and protection was prolonged. This may be explained by previous data in the literature showing that Intralipid affects the reticuloendothelial system of the recipient. Conclusions: The evidence suggests that Intralipid might be an effective treatment for human recurrent miscarriages, and injection into women who may become pregnant has been found ethically acceptable at one university center. Comparison of Intralipid to partner leukocyte immunotherapy or IVIG would be worthwhile. For adequate statistical power, this would require a large, multicenter, prognostically stratified randomized controlled trial and could be accomplished via the Recurrent Miscarriage Immunotherapy Trialists Group network.

16/7/17 (Item 4 from file: 73)
DIALOG(R)File 73:EMBASE


05276767 EMBASE No: 1993044852
Immune reproductive failure: Effect of nonspecific immunostimulation in mouse model
Strassburger D.; Carp H.; Toder V.
Department of Embryology/Teratology, Sackler School of Medicine, Tel-Aviv University,Ramat-Aviv 69978 Israel
American Journal of Reproductive Immunology ( AM. J. REPROD. IMMUNOL. ) ( Denmark) 1992, 28/3-4 (274-276)
CODEN: AAJID ISSN: 8755-8920
DOCUMENT TYPE: Journal; Conference Paper
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH

There is much evidence that pregnancy loss may be immunologically mediated. Failure of the maternal immune system to actively support the pregnancy may be responsible for its demise. Potentiation of immune functions has been attempted in humans; however, the success of immunotherapy is still not clear. Thus immunotherapy experiments in mouse models are important. Nonspecific immunostimulation with complete Freund adjuvant (CFA) was shown in our laboratory to reverse the tendency to fetal loss in the CBA/J x DBA/2J mouse combination. CFA elevates the non-T lymphocyte population, decreases T- cell secreted lymphokines, and enhances macrophage-secreted monokines. However, a relationship between these changes and a beneficial effect of CFA on reproductive performance has to be proved. Information obtained from nonspecific immunopotentiation in the CBA/J-DBA/2J model may contribute the assessment of nonspecific immunotherapy in humans.

16/7/18 (Item 5 from file: 73)
DIALOG(R)File 73:EMBASE


04817476 EMBASE No: 1991312212
Mouse model for the treatment of immune pregnancy loss
Toder V.; Strassburger D.; Carp H.; Irlin I.
Department of Embryology, Tel-Aviv University, Medical School,Ramat-Aviv 69978 Israel
American Journal of Reproductive Immunology ( AM. J. REPROD. IMMUNOL. ) ( Denmark) 1991, 26/1 (42-46)
CODEN: AAJID ISSN: 8755-8920
DOCUMENT TYPE: Journal; Conference Paper
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH

Spontaneous abortions can be associated with preimplantation embryo loss, implantation problems and a variety of postimplantation pregnancy failures. The long list of possible causes for the postimplantation pregnancy loss includes, among others, genetic abnormalities in fetus, anatomical abnormalities of the uterus, endocrinological insufficiency, and microbiological problems. However, more than 50% of recurrent miscarriages still have no recognized causes. The concept that many such abortions may be immunologically mediated has gained increasing support over the years. Moreover, immunization of such women with husband's or third party leukocytes has resulted in more than 70% of subsequent pregnancies resulting in live births. Since neither the mechanisms leading to pregnancy loss nor the success of immunotherapy are clear, the set-up of animal models for recurrent abortions would be of supreme significance. Our recent data show that immunopotentiation of maternal immune system by Complete Freund Adjuvant significantly improves pregnancy rate in CBA x DBA/2 mouse combination with high percentage of fetal resorptions. This effect is

followed by decrease of IL 2 production in spleen; increase of MAC 1-positive cells at placenta; amplification of suppressive activity of local and systemic lymphocytes and by reverse of embryotoxic effect of maternal serum. Data obtained in this model seems to be valuable in substantiation of rationale for nonspecific immunotherapy of human abortions.

16/7/19 (Item 1 from file: 155)
DIALOG(R)File 155:MEDLINE(R)


09649944 21438480 PMID: 11554693
Activation of the novel prothrombinase, fg12, as a basis for the pregnancy complications spontaneous abortion and pre-eclampsia.
Knackstedt M; Ding J W; Arck P C; Hertwig K; Coulam C B; August C; Lea R; Dudenhausen J W; Gorczynski R M; Levy G A; Clark D A
Toronto General Hospital Research Institute, University of Toronto, Ontario, Canada.
American journal of reproductive immunology (New York, N.Y. - 1989) ( Denmark) Sep 2001, 46 (3) p196-210, ISSN 1046-7408 Journal Code: 8912860
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
PROBLEM: Impaired trophoblast invasion during the first trimester of pregnancy is linked to spontaneous abortion, and defective invasion in the second trimester to hypertension + proteinuria (pre-eclampsia). Hypertension developing during the third trimester of human pregnancy represents, in part, a corrective response in the mother to provide adequate placental perfusion for fetal growth when trophoblast has not to invaded and converted the myometrial porprtion of maternal spiral arteries into to low resistance-high capacitance conduits. Deportation of vesicles from hypoxemic trophoblast is thought to cause hypertension plus proteinuria, vascular damage and a systemic coagulopathy. Trophoblast invasion may be inhibited by local cytokines, such as TGF-betas but Thl-type cytokines associated with pre-eclapmsia and spontaneous abortions (e.g., IL-1, TNF-alpha, IFN-gamma) are not known to inhibit migration at in situ concentrations. Trophoblast invasion is also inhibited by the binding of surface integrins to fibronectin and fibrin, and fibrin production is stimulated by these Th1 cytokines via up-regulation of prothrombinases(s) such as fg12 which directly and via TNF-alpha-facilitated inflamation compromise trophoblast cell integrity. We, therefore, asked if fg12 expression and TNF-alpha are increased in first trimester human miscarriage and in third trimester pre-eclampsia. METHODS: fg12 mRNA was detected using in situ hybridization and fg12 protein by immunohistochemistry. TNF-alpha mRNA and protein were similarly tested. The techniques were validated using uterine sections from day 8.5 of CBA x DBA/2 pregnancies, and then were applied to sections of placentae from normal and pre-eclamptic pregnancies with and without intrauterine fetal growth restriction (IUGR). Fibrin was detectectd by immunohistochemistry. RESULTS: Expression of fg12 protein correlated with fg12 mRNA expression in mouse uteri and in placentae from normal human pregnancies. Increased expression of fg12 and TNF-alpha mRNA and protein, and increased fibrin deposition was detected in placental trophoblast. CONCLUSIONS: Activation of fg12 prothrombinase by Th1-type cytokines in pregnancy may lead to spontaneous abortion, or in ongoing pregnancy, to pre-eclampsia and/or IUGR.
Record Date Created: 20010913
Record Date Completed: 20020307
? ds

Set Items Description

S1 707 (SPONTANEOUS(W)A TION) AND MODEL?
S2 590 S1 AND HUMAN?
S3 109 S2 AND (CORRELAT? OR PREDICT?)
S4 72 RD S3 (unique items)
S5 4 S4 AND (DBA?)
S6 4 RD S5 (unique items)
S7 0 (SPONTANEOUS(W)ABORTION)(20N)(MURINE OR MOUSE) AND (CORREL-AT? OR PREDICT?)(10N)(HUMAN)
S8 7 (SPONTANEOUS(W)ABORTION)(20N)(MURINE OR MOUSE) AND (CORREL-AT? OR PREDICT?) AND (HUMAN)
S9 5 RD S8 (unique items)
S10 22 (SPONTANEOUS(W)ABORTION)(20N)(MURINE OR MOUSE) AND (MODEL?) AND (HUMAN)
S11 20 RD S10 (unique items)
S12 12 SPONTANEOUS(W)ABORTION AND MISCARRIAGE AND DBA?
S13 6 RD S12 (unique items)
S14 117 SPONTANEOUS(W)ABORTION AND DBA?
S15 58 RD S14 (unique items)
S16 19 S15 AND HUMAN?

# WEST Search History

DATE: Wednesday, August 06, 2003

| Set Name side by side | Query | Hit Count | Set Name result set |
|---|---|---|---|
| *DB=USPT,PGPB,DWPI; THES=ASSIGNEE; PLUR=YES; OP=OR* | | | |
| L9 | L2 and (@RLAD<19971110 or @pd<19971110) | 25 | L9 |
| L8 | L2 and (@RLAD<19981110 or @pd<19971110) | 26 | L8 |
| L7 | L6 and (@RLAD<19981110 or @pd<19971110) | 1425 | L7 |
| L6 | (immune or immunological or co-stimulat$ or costimlat$) same (fertil$ or abort$ or pregna$) | 2659 | L6 |
| L5 | (immune or immunological or co!stimulat$) same (fertil$ or abort$ or pregna$) | 34836 | L5 |
| L4 | (immun$ or co!stimulat$) same (fertil$ or abort$ or pregna$) | 36712 | L4 |
| L3 | L1 and (@RLAD<19981110 or @pd<19971110) | 236 | L3 |
| L2 | L1 and (fertil$ or abort$ or pregna$) | 41 | L2 |
| L1 | OX-2 or OX2 or CD200 | 394 | L1 |

END OF SEARCH HISTORY